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Cimetidine and Cytopenia

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A NUMBER OF REPORTS have recently described cimetidine-associated granulocytopenia, some with documented bone marrow depression.[1-3] In addition, cimetidine-associated thrombocytopenia has been described.[4,5] Since the first widely used histamine H_2 receptor antagonist, metiamide, was withdrawn from clinical use because of related agranulocytosis, concern has arisen that cimetidine may also have adverse hematologic effects.

Review of the reported cases of cimetidine-associated cytopenia suggests that a prerequisite to this complication may be preexisting compromise of bone marrow stem cell reserves. However, there have been no specific experimental data pertaining to this hypothesis.

We describe two cases of cimetidine-related granulocytopenia, one accompanied by thrombocytopenia, and report the results of in vitro bone marrow tissue cultures and antibody detection studies carried out to attempt elucidation of the mechanism of cimetidine toxicity.

Reports of Cases

CASE 1. A 78-year-old white man was admitted to Cedars-Sinai Medical Center in February 1979 with stomatitis, perirectal ulcerations and fever.

Eight months earlier, chronic lymphocytic leukemia was diagnosed and was treated with chlorambucil (oral administration of 4 mg per day for five days and then 2 mg per day for five days) and prednisone. Thereafter, his leukemia required no further treatment. Four months later, he was admitted to hospital because of gastrointestinal hemorrhage. No bleeding site was found by either endoscopic or radiographic methods and intravenous vasopressin therapy successfully controlled the hemorrhage. He was discharged on a regimen of 300 mg of cimetidine given orally four times a day for presumed radiologically inapparent peptic ulcer disease.

A month later, in November 1978, exfoliative dermatitis developed. Biopsy of the skin lesions showed no leukemic involvement. Administration of prednisone, 60 mg orally every other day, was begun and the dermatitis resolved; however, discontinuation of treatment after a month resulted in recurrence of the dermatitis. Reinstitution of prednisone in the same dosage led to improvement. This treatment was gradually tapered and finally stopped several weeks before his admission to Cedars-Sinai Medical Center.

Three weeks before admission, the patient's cell count included the following: hemoglobin 13.3 grams per dl, hematocrit 39 percent and leukocyte count 12,700 per cu mm, with 31 percent neutrophils, 1 percent band forms and 68 percent lymphocytes; platelet count was 170,000 per cu mm.

During the three weeks before admission, he experienced oral discomfort, rectal pain and tenesmus. Fevers and sweats occurred during the two weeks before admittance to hospital. Ulcers of the tongue developed, and the patient experienced increasing difficulty in swallowing. During the week before admission, progressive weakness was noted. No easy bruising, bleeding or lymph node enlargement occurred. There was no history of recent respiratory infection, hepatitis, connective tissue disease or exposure to chemical toxins. He had taken no medications other than cimetidine and the recent course of prednisone.

Physical examination on admission showed a cachectic, dehydrated man. The temperature was 39°C (102.2°F). His skin was anicteric and showed mild exfoliative dermatitis on all four extremities. No lymph node enlargement was noted. The oral mucosa was clear, but on the tongue there were two exquisitely tender ulcers (each 1 cm in diameter), with yellow depressed centers and indurated borders. There was no enlargement of the liver or spleen. Rectal examination showed a 1-cm perianal ulcer with a yellow center and indurated border, a rectocutaneous fistula and induration of the rectal mucosa.

Laboratory data included the following: hemoglobin 12.9 grams per dl, hematocrit 37.2 percent, normal erythrocyte indices and leukocyte count

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3,200 per cu mm, with 1 percent neutrophils, 90 percent lymphocytes, 6 percent atypical lymphocytes and 3 percent monocytes; platelet count was 420,000 per cu mm. Prothrombin time, partial thromboplastin time, serum protein electrophoresis and creatinine values were within normal limits.

A bone marrow aspirate and biopsy specimen showed the marrow to be 80 percent cellular; 90 percent of the cells were lymphocytes. The megakaryocytes appeared normal. The granulocytic series was substantially reduced in number with a pronounced shift to the left and only rare early precursors. Erythroid maturation was normoblastic.

Cimetidine therapy was discontinued on the patient's admission, and administration of gentamicin, carbenicillin and nafcillin was begun for presumed unidentified bacteremia. Local care was given for the ulcers and topical nystatin was prescribed for oral and esophageal candidiasis. He was given granulocyte transfusions the morning after admission, and these were continued daily for the next ten days.

He defervesced during the first 48 hours after admission. After two weeks in hospital, small numbers of monocytes, followed by band forms, and then polymorphonuclear neutrophils, appeared in the peripheral blood smears, and by the middle of the third hospital week the granulocyte counts had returned to normal (Figure 1).

A bone marrow aspirate and biopsy specimen obtained on the 20th hospital day showed 80 percent cellularity. The megakaryocytes were slightly increased in number. The granulocytic series showed complete and normal maturation. The erythroid line was slightly hyperplastic with normoblastic maturation, and the myeloid to erythroid ratio was 3:1. Mature lymphocytes were increased in number, with a diffuse pattern including occasional small nodules, and comprised about 50 percent of the total cellularity.

In Vitro Studies

Tissue from the patient's marrow obtained during his recovery (hospital day 20) and from marrows of healthy volunteers were cultured in vitro in the presence of cimetidine. The marrow samples were cultured with and without the patient's serum collected at the nadir of his granulocytopenia (on admission) and with complement, to assess, respectively, both immune-mediated and direct cimetidine toxicity. When assayed for committed granulocyte-monocyte progenitor cells (operationally, colony-forming units—culture [CFU-C]),[6] the patient's marrow showed no increased sensitivity to cimetidine when compared with the control marrows, nor did the patient's serum (during acute phase) show any cimetidine-mediated suppressive effects. (Control range 40 to 130 CFU-C per 2×10^5 tested marrow cells; patient 48 CFU-C per 2×10^5 tested marrow cells. Control and patient's marrow cultures were equally suppressed by 500, 750 and 1,000 μg per ml concentrations of ci-

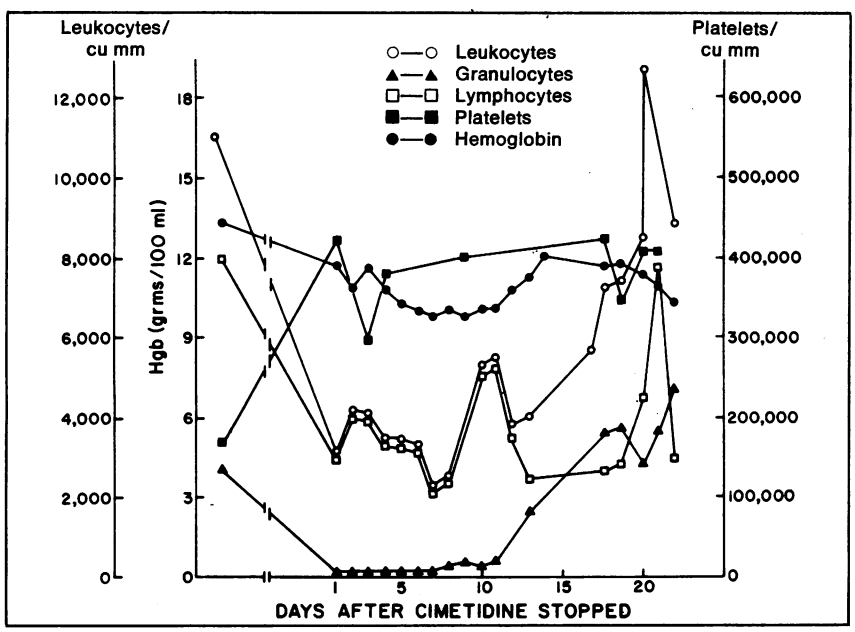

Figure 1.—Blood cell counts for patient 1. Cimetidine was stopped on the first hospital day; the first illustrated blood count was obtained three weeks earlier.

metidine, which represented approximately 100 times the usual peak therapeutic serum levels.)

CASE 2. A 57-year-old white woman with a 20-year history of peptic ulcer disease was admitted to Cedars-Sinai Medical Center in March 1979 because of oropharyngeal hemorrhagic vesicles and purpura.

Ten days before admission she experienced palpitations and took two or three quinidine tablets, which she had taken for several months a year previously. No further quinidine was taken after she visited her physician that day.

Seven days before admission, she returned to her physician because of recurrence of her typical ulcer pain. Administration of cimetidine, 300 mg orally three times a day, was prescribed and relief of her symptoms occurred within 48 hours.

During the two days before admission hemorrhagic blebs developed, first on the lips and then on the oropharyngeal mucosa and tongue. On the day of admission, she awoke with purpura over her entire body.

She stated that she had no previous history of bleeding, easy bruising, lymph node enlargement, recent upper respiratory tract infection, hepatitis, renal disease or connective tissue disorder. She had ingested no quinine-containing beverages and had no history of exposure to chemical toxins. Her most recent blood cell count, done several months earlier, included hemoglobin 11.9 grams per dl, hematocrit 36.0 percent and leukocyte count 5,400 per cu mm, with 54 percent neutrophils, 43 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils; adequate platelets were noted. Her other medications included conjugated estrogens, USP 0.625 mg taken orally 15 days per month for menopause symptoms, and acetaminophen, 325 mg taken orally several times a week for headaches.

She was afebrile on admission. On physical examination, small purpuric areas over all four extremities and confluent petechiae on her legs and ankles were noted. Hemorrhagic bullae were present on the oropharyngeal mucosa, tongue and lips. There was no enlargement of lymph nodes, liver or spleen.

On admission, laboratory data included the following: hemoglobin 15.0 grams per dl, hematocrit 43.0 percent, normal erythrocyte indices and leukocyte count 2,100 per cu mm, with 54 percent neutrophils, 43 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils; platelet count was 2,000 per cu mm. Prothrombin time, partial thromboplastin time, serum protein electrophoresis and creatinine values were within normal range. No quinidine was detected in her serum. Her serum muramidase value was normal, and Coombs, sucrose hemolysis and mononucleosis spot tests were negative. Assays for hepatitis B surface antigen, rheumatoid arthritis latex factor, antinuclear antibodies and lupus erythematosus cells were all negative.

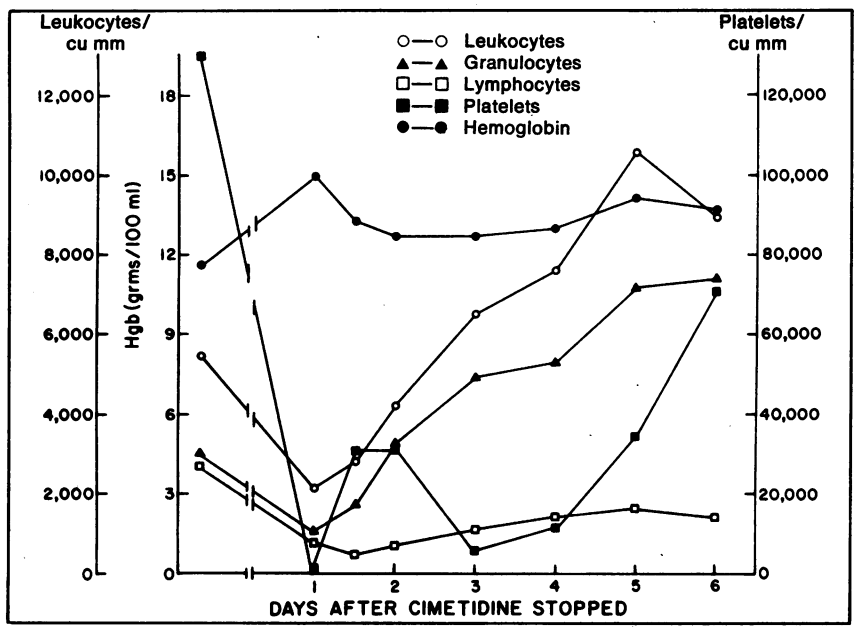

Figure 2.—Blood cell counts for patient 2. Cimetidine was stopped on the first day in hospital; the first illustrated blood cell count was obtained three months earlier.

A bone marrow aspirate and biopsy, obtained at the time of admission, showed slight hypocellularity and mild megakaryocytopenia. There was a pronounced shift to the left in the granulocytic series, with a predominance of young forms and rare fully segmented cells. Erythroid maturation was normoblastic, and the myeloid to erythroid ratio was 2:1. The lymphocytes were normal.

On admission, all medications were discontinued, and the patient was given platelet transfusions and 40 mg of methylprednisolone intravenously followed by 40 mg of prednisone orally twice a day. Antacids were administered orally for peptic ulcer disease. During the next several days, the leukocyte count returned to normal; during the next week, the platelet count returned to normal as well (Figure 2).

A bone marrow aspirate obtained 11 days after admission showed normocellular marrow with normal maturation of the granulocytic series and normal numbers of megakaryocytes. Erythroid maturation was normoblastic and the myeloid to erythroid ratio was 3:1.

In Vitro Studies

To investigate the role of drug-related antibody-mediated platelet destruction, the patient's serum, collected at the nadir of her thrombocytopenia (pretreatment, on admission), was tested in vitro in the presence of normal donor platelets and was compared with normal control serum. Using the radioactive chromium (^{51}Cr)-labeled platelet lysis method (with complement),[7] donor platelets lysed in combination with the patient's serum without the addition of quinidine or cimetidine. A positive reaction for antibodies in the absence of either drug was also obtained by the fluorescent antibody technique,[8] confirming the presence of sufficiently high serum antibody activity to prevent detection of specific drug-dependent antibodies.

Platelet antibody studies were repeated using serum collected after return of the blood counts to normal (day 11). Using the fluorescent antibody technique, recovery serum tested positive for antibody each with cimetidine (+) and quinidine (+++) (maximum positive [++++]), while serum alone tested negative.

To test for antibody-mediated as well as direct bone marrow toxicity, cimetidine and quinidine were each incubated with marrow tissue cultures, with and without the patient's serum, at the nadir of the cytopenia (pretreatment, day 1); the cultures were assayed for granulocyte-monocyte progenitor cells (CFU-C).[6] The patient's marrow showed no increased sensitivity to quinidine or cimetidine, with or without acute-phase serum and complement, when compared with control cultures from normal human marrow. (Control range 40 to 130 CFU-C per 2×10^5 tested marrow cells; patient 75 CFU-C per 2×10^5 tested marrow cells. The marrow specimens of the patient and the controls were suppressed equally at 500, 750 and 1,000 μg per ml of cimetidine, approximately 100 times the usual peak therapeutic serum levels.)

Comments

Metiamide, the first widely used histamine H_2 receptor antagonist, was effective in treatment of hypersecretory upper gastrointestinal disorders, but it was withdrawn from clinical use following reports of associated agranulocytosis.[9,10] Cimetidine, which differs from metiamide by replacement of the thiourea side chain with a cyanoguanidine moiety, did not show bone marrow suppression in animal and clinical trials,[11,12] and it has become widely used in the treatment of peptic ulcer disease and Zollinger-Ellison syndrome. Reversal of metiamide-induced bone marrow suppression and agranulocytosis after replacing metiamide with cimetidine,[9] and a report of cimetidine tolerance by a patient in whom a metiamide-related agranulocytosis had developed six months earlier,[10] have been advanced as evidence that metiamide bone marrow toxicity is unique to that compound.[13] Further, it has been suggested that the elimination of the thiourea group in cimetidine may be the reason for the lack of marrow toxicity found with metiamide.[14] In vitro, radioactive hydrogen (^3H)-labeled metiamide, like radioactive sulfur (^{35}S)-labeled thiourea, is retained by a variety of bone marrow cells, while there is no (^3H)-labeled cimetidine uptake.[15] This suggests that metiamide, with its thiourea side chain, may more easily gain *access* to the stem cell to effect its toxicity. Indeed, the actual *mechanisms* of toxicity of metiamide and cimetidine may not differ. Reports by Byron describing in vivo bone marrow experiments suggest that the action of metiamide may be histamine H_2 receptor-mediated and, thus, may be common to both drugs.[16-18] Using the mouse pluripotent stem cell (CFU-S) assay, he demonstrated that H_2 receptor-mediated stimulation of stem cell division can be blocked by both metiamide and cimetidine.

The bone marrow biopsy specimens obtained

from both of our patients at the time of acute granulocytopenia showed marrow depletion of the granulocytic series. The bone marrow tissue culture studies showed no cimetidine-mediated (antibody-mediated or direct) depression of granulocyte progenitor cell activity (CFU-C) in our patients' marrow specimens when compared with marrow specimens from normal controls. Although necessarily limited by the sensitivity of in vitro study,[19] these results showed that our patients had no unusual intrinsic sensitivity to drug-mediated bone marrow toxicity. Most consistent with our data and other reported cases of cimetidine-associated cytopenia, as suggested by Byron,[18] Freston[3] and Selker and colleagues,[25] is the possibility that cimetidine has a generalized effect on marrow stem cells that may become manifest as peripheral cytopenia when another insult has already caused preexisting progenitor cell reserve depletion. It seems likely that our patients had reduced stem cell reserves at the time of cytopenia. The first patient had leukemia and also had received the alkylating agent chlorambucil; both of these factors can reduce granulocyte precursor reserves.[20,21] The longer duration of granulocytopenia in this patient may have been related to a more severe underlying marrow derangement and also to ongoing additional marrow reserve depletion by concomitant sepsis.[22] As demonstrated by the antibody detection studies, the second patient had an ongoing destructive immune process (thrombocytopenia), which also can cause stem cell reserve depletion.[23,24] The possibility that cimetidine toxicity is related to the presence of underlying marrow injury is additionally supported by the observation of substantially more severe nadirs of granulocytopenia in six of eight patients receiving cimetidine concomitantly with carmustine (BCNU) chemotherapy for brain tumors than in patients in a large group not receiving prophylactic cimetidine.[25] Also consistent with this is a recent report describing a patient treated with methotrexate in whom reproducible cimetidine-associated severe granulocytopenia developed.[26] Indeed, nearly all of the previously reported cases of cimetidine-associated granulocytopenia have included coexisting processes that are known to reduce bone marrow reserves such as sepsis, immune diseases, renal failure or hematologic malignancies.

The cause of thrombocytopenia in case 2 is uncertain from our experiments and may be multifactorial. Because the serum collected on admission caused donor platelet lysis without added drug, it is likely that she had either antiplatelet antibodies or already formed immune complexes in the circulation during the time of the acute cytopenia. Because her serum specimens during convalescence showed both cimetidine-dependent and quinidine-dependent antibody activity, the relative roles of the two drugs cannot be well assessed. Although the possibility of primarily quinidine-related thrombocytopenia cannot be eliminated, the ten-day delay after ingestion is somewhat atypical, and the decreased, rather than increased, number of bone marrow megakaryocytes argues against typical quinidine-immune thrombocytopenia. However, these observations are consistent with a suppressive effect on bone marrow megakaryocytes by cimetidine with a concomitant immune process affecting the megakaryocyte line, which in turn causes an effect on platelet precursors essentially analogous to the situation proposed above for the granulocytic line. Further, this is consistent with two other reported cases of cimetidine-associated thrombocytopenia, in which there were additional concomitant causes of thrombocytopenia (immune thrombocytopenia associated with systemic lupus erythematosus in one and alcohol abuse in the other).[4,5,24,27]

Cimetidine, having been used by about 11 million patients, has been associated with leukopenia at an approximate rate of one per 100,000 and agranulocytosis in approximately one in three million (Unpublished data, M. L. Gifford, Director of Medical Affairs, Smith Kline & French Laboratories, Philadelphia, Dec 1980). (A summary of all reported cases of cimetidine-associated cytopenia is presented in Table 1.)

Bone marrow suppression was noted in marrow biopsy specimens in approximately 1 percent of patients with peptic ulcer disease who were taking metiamide,[12] despite the far less frequent occurrence of agranulocytosis. This supports the possibility that inapparent degrees of modulation of the pleuripotent stem cell by H_2 receptor antagonists may be more frequent than are noted clinically. Bone marrow suppression by cimetidine may only become significant enough to alter the circulating cell populations in patients who already have compromised or stressed stem cell reserves, as was likely in the two cases reported here. This possibility reinforces the need for restricting the use of this drug to established indications, and particularly suggests the need for monitoring hematologic values in patients having diseases or

TABLE 1.—*Summary of 25 Cases of Cimetidine-Associated Cytopenia*

Authors and Ref. No.	*Patient's Age*	*Peripheral Blood Count at Nadir (10^3/cu mm)* Leukocytes	Granulocytes	Platelets	*Clinical Problem*	*Possible Marrow-Suppressing Condition*	*Other Medications*
		(First exposure)					
Carloss et al[26]	67	2.2	0.022	217	Pyloric ulcer, psoriasis	Methotrexate	Furosemide, spironolactone, retinoic acid
		(Re-exposure)					None during reexposure
		2.4	0.048	*			
Corbett & Holdsworth[28]	44	2.7	1.80	*	Duodenal ulcer, urinary tract infection	? Sepsis	Sulfamethoxazole-trimethoprim
Chang & Morrison[29]	66	0.30	0.0	186	Gastric ulcers	*Klebsiella* and streptococcal sepsis	Dioctyl calcium sulfosuccinate
Craven & Whittington[30]	28	2.2	0.022	205	Duodenal ulcer	None noted	Metoclopramide, acetaminophen, penicillin V, poldaine methylsulfate
Idvall[5]	75	*	*	19	Gastric ulcer	None noted	"None suspicious for cytopenia"
	57	*	*	20	History of peptic ulcer, liver failure	Alcohol abuse, liver failure	"None suspicious for cytopenia"
Isaacs[31]	43	6.6	4.01	6	Gastric ulcer	Sarcoidosis	Prednisolone
James & Prout[2]	41	3.0	*	30	Hematemesis	Proteus sepsis	Gentamicin, ampicillin
Johnson et al[32]	39	2.8	1.6	100	Duodenal ulcer, *Salmonella* gastroenteritis	? Sepsis	*
Klotz & Kay[33]	62	3.1	1.86	57	Antral gastritis, arthritis	Autoimmune thrombocytopenia	Hydrochlorothiazide, propranolol, levothyroxine, prednisone
Lopez-Luque et al[1]	29	2.3	1.41	*	Duodenal ulcer, hypertension, fever	None noted	Tranexamic acid, clorazepate
McDaniel & Stein[4]	77	*	*	24	Chronic obstructive lung disease, cecal carcinoma, history of ulcer disease	Carcinoma	Corticosteroids
Posnett et al[34]	43	1.7	0.62	120	Gastric ulcer	Lymphoma	Dioctyl calcium sulfosuccinate
Rate et al[35]	53	3.1	1.86	57	Gastritis, cryptogenic cirrhosis	Hemolytic anemia	*
Sazie & Jaffe[36]	17	1.4	0.12	"Normal"	Subdural hematoma, staphylococcal bacteremia	Phenytoin	Phenytoin, tobramycin, dexamethasone
Selker et al[25]†	..(six patients)	<0.5	*	<8	Brain tumors (GI prophylaxis: see text)	Carmustine	*
Ufberg et al[14]	62	1.3	0.026	77	Duodenal ulcer, hypertension, renal failure	Uremia	Digoxin, clonidine
Wallin et al[37]	78	2.4	0.0	240	Upper GI bleeding, cirrhosis	Phenytoin, alcohol abuse	Phenytoin (for 20 years), spironolactone, tobramycin, cefazolin
Present cases	78	3.2	0.032	420	Presumed ulcer disease	Chronic lymphocytic leukemia; prior chlorambucil treatment	Prednisone
	57	2.1	1.10	2	Duodenal ulcer	Immune thrombocytopenia	Estrogens, acetominophen, prior quinidine

GI = gastrointestinal

*Not specified
†Data cover six patients in study. All six had <0.5 leukocytes, granulocytes not specified and <8 platelets (10^3/cu mm), brain tumors and carmustine therapy.

receiving treatments associated with depressed bone marrow reserves.

Summary

Cimetidine-associated granulocytopenia was observed in two patients, one with concomitant thrombocytopenia and both with probable underlying bone marrow reserve compromise. In vitro bone marrow cultures from these patients did not differ from control marrows in sensitivity to cimetidine when assayed for granulocyte-monocyte progenitor cells (CFU-C). Platelet antibody studies showed evidence for drug-mediated thrombocytopenia in one patient, but there was evidence also for primary bone marrow megakaryocyte suppression. The data from these patients suggest that there may be a generalized bone marrow suppressive effect of cimetidine, which becomes manifest as peripheral cytopenia only when a significant preexisting insult has caused marrow stem cell reserve depletion. This hypothesis is discussed in light of other experimental data and other reported cases of cimetidine-associated cytopenia.

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